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(54) Title: NEW USES

(57) Abstract: The present invention relates to the treatment of conditions associated with cephalic pain such as migraine, cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorders, headache associated with substances or their withdrawal, rebound headache and tension headache. In particular it relates to the use of a $5HT_1$ receptor agonist in combination with an analgesic and an anti-emetic and/or gastroprokinetic agent.

New Uses

The present invention relates to the treatment of conditions associated with cephalic pain such as migraine, cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorders, headache associated with substances or their withdrawal, rebound headache and tension headache. In particular it relates to the use of a $5HT_1$ receptor agonist in combination with an analgesic and an anti-emetic and/or gastroprokinetic agent.

$5HT_1$ receptor agonists are well known in the art and the term is to be broadly understood to include $5HT_1$ receptor agonists of all types including, but not limited to, $5HT_1$-like receptor agonists, $5HT_{1B}$ receptor agonists, $5HT_{1D}$ receptor agonists and $5HT_{1F}$ receptor agonists. Particular reference is made to the compounds sumatriptan (described for example in GB Patent No. 2162522, incorporated herein by reference), naratriptan, rizatriptan, zolmitriptan, frovatriptan, eletriptan, almotriptan, avitriptan, donitriptan, alniditan, ALX-0646, LY334370, U1092291, IS159 and PNY142633.

Numerous clinical studies have demonstrated the effectiveness of sumatriptan in migraineurs. However, some migraineurs do not respond to treatment with sumatriptan alone.

In some forms of migraine, certain patients have found total or partial relief with the use of analgesics such as paracetemol and phenacetin. However, it has been reported (WO98/06392) that analgesics, when taken alone, are rarely effective in providing complete and rapid relief of all the symptoms of migraine, but that with a combination therapy of $5HT_1$ receptor agonists and analgesics, their effectiveness is increased.

Oral administration constitutes the generally preferred route for administration of pharmaceuticals since this route is particularly convenient and acceptable to patients. Unfortunately, oral compositions may be associated with certain

disadvantages in the treatment of conditions associated with cephalic pain. For example, such conditions, particularly migraine, are associated with nausea, vomiting and gastrointestinal dysfunction in the form of delayed gastric emptying.

Von Seggern et al. (headache, 1996, 493 – 502) describes the possiblity of "triple therapy" combining metoclopramide, an NSAID and an ergotamine preparation for the treatment of acute migraine. However, there is no suggestion that sumatriptan could be used in such a triple combination.

GB2325161 discloses the use of an anti-emetic and/or gastroprokinetic agent in combination with a $5HT_{1B/1D}$ receptor agonist for the treatment of the nausea and vomiting associated with migraine. There is no suggestion that such a combination improves the efficacy of the $5HT_{1B/1D}$ agonist as an anti-migraine treatment.

WO00/25778 discloses the combined use of metoclopramide and $5HT_1$ agonists for the acute treatment of migraine and states that such a combination provides enhanced efficacy and less nausea but provides no data to substantiate such statements.

US6077539 describes the use of a specific dosage form comprising rapid availability metoclopramide and a long-acting NSAID for the treatment of migraine. The formulation is absent any $5HT_1$ receptor agonist agent in order to avoid any "negative side effects linked to excessive vasoactivity in regions of the body not involved in the pathogenesis of migraine."

Further, it has been shown in human volunteers that a combination of zolmitriptan, paracetamol and metoclopramide caused no clinically significant changes in the bioavailability or absorption of the three drugs.

Thus, it could be concluded that a triple combination of a $5HT_1$ receptor agonist, analgesic and anti-emetic and/or gastroprokinetic would have no clinical advantage over the dual combination of a $5HT_1$ receptor agonist plus an analgesic, the dual combination of a $5HT_1$ receptor agonist plus an anti-emetic and/or gastroprokinetic agent, or the dual combination of an analgesic and an anti-emetic and/or gastroprokinetic agent.

However, a medicament to overcome the delayed gastric emptying as well as providing complete and rapid relief of all the symptoms of migraine would be advantageous.

It has now surprisingly been found that the use of a $5HT_1$ receptor agonist in combination with an analgesic and an anti-emetic and/or gastroprokinetic agent is effective in the treatment of conditions associated with cephalic pain.

Thus, the present invention provides, in one aspect, the use of a $5HT_1$ receptor agonist, or a pharmaceutically acceptable derivative thereof, with an analgesic or a pharmaceutically acceptable derivative thereof, and an anti-emetic and/or gastroprokinetic agent, or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for oral administration for use in the treatment of conditions associated with cephalic pain.

By pharmaceutically acceptable derivative is meant any pharmaceutically acceptable salt, solvate, ester or amide, or salt or solvate of such ester or amide, of the $5HT_1$ receptor agonist, the analgesic or the anti-emetic and/or gastroprokinetic agent, or any other compound which upon administration to the recipient is capable of providing (directly or indirectly) the $5HT_1$ receptor agonist, the analgesic or the anti-emetic and/or gastroprokinetic agent or an active metabolite or residue thereof.

Suitable pharmaceutically acceptable salts according to the invention include acid addition salts formed with inorganic acids such as hydrochlorides,

hydrobromides, phosphates and sulfates and with organic acids, for example tartrates, maleates, fumarates, succinates and sulfonates.

The combinations of the invention may also be useful as analgesics. They may be used to improve the condition of a host, typically of a human being, suffering from pain. They may be employed to alleviate pain in a host. Thus, the combinations of the invention may be used as a preemptive analgesic to treat acute pain such as muscculoskeletal pain, post operative pain and surgical pain, chronic pain such as chronic inflammatory pain (e.g. rheumatoid arthritis (RA) and osteoarthritis (OA), neuropathic pain (e.g. post herpetic neuralgia (PHN), trigeminal neuralgia, neuropathies associated with diabetes and sympathetically maintained pain) and pain associated with cancer and fibromyalgia. The combinations of the invention may also be used in the treatment or prevention of pain associated with Functional Bowel Disorders (e.g. Irritable Bowel Syndrome), non cardiac chest pain and non ulcer dyspepsia.

Suitable $5HT_1$ receptor agonists for use according to the invention include sumatriptan, naratriptan, zolmitriptan, eletriptan, rizatriptan, frovatriptan, almotriptan, avitriptan, donitriptan, alniditan, ALX-0646, LY334370, U1092291, IS159 and PNY142633. Naratriptan and sumatriptan are preferred, with sumatriptan being particularly preferred. A preferred form of sumatriptan is the succinate salt, particularly the 1:1 succinate. The $5HT_1$ receptor agonists may be used alone or in combination with each other.

Analgesics are well known in the art. Suitable analgesics for use according to the invention include adenosine A1 receptor agonists, opioids, para-aminophenol derivatives and non-steroidal anti-inflammatory drugs (NSAIDs). A1 receptor agonists have been described in the art and include compounds described in the published patent applications WO99/24449, WO99/24450, WO99/24451, WO97/43300, WO98/16539, WO98/04126, WO98/01459, EP0322242, GB2226027, EP222330, WO98/08855, WO94/0707 and WO99/67262. Opioids include alfentanil, buprenorphine, codeine,

dextropropoxyphene, diamorphine, dihydrocodeine, fentanyl, methadone, morphine, oxycodone, levorphanol, pentazocine, pethidine, nefopam, flupirtin, meptazinol and tramadol. Para-aminophenol derivatives include paracetamol (also known as acetaminophen), propacetamol, phenacetin and acetanilide. NSAIDs include naproxen, ibuprofen, flurbiprofen, ketoprofen, dexketoprofen, fenoprofen, fenbufen, tolfenamic acid, mefenamic acid, tiaprofenic acid, indomethacin, oxaprozin, diclofenac, aceclofenac, sulindac, ketorolac, nabumetone, phenylbutazone, azapropazone, diflunisal, piroxicam, tenoxicam, salicylates such as aspirin, and COX-2 inhibitors such as celecoxib, rofecoxib, valdecoxib, parecoxib, JTE-522, etoricoxib (MK663), nimesulide, flosulide, COX189, etodolac, meloxicam, DFP, NS398, L-745337, 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine, 8-acetyl-3-(4-fluorophenyl)-2-(4-methanesulfonylphenyl)-imidazo[1,2-a]pyridine, 4-[2-(3-fluorophenyl)-6-trifluoromethyl-pyrazolo[1,5-a]pyridin-3-yl]-benzenesulfonamide and N-isobutyl-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidin-2-amine. Particularly suitable analgesics for use according to the invention are aspirin, naproxen, ibuprofen, paracetamol, and their pharmaceutically acceptable salts or solvates. Aspirin is especially suitable. The analgesics may be used alone or in combination with each other.

Suitable anti-emetic and/or gastroprokinetic agents for use according to the invention include alizapride, alosetron, azasetron, batanopride, bemesetron, benzquinamide, bietanautine, bromopride, buclizine, chlorpromazine, cinitapride, cisapride, clebopride, cyclizine, dimenhydrinate, diphenidol, dolasetron, domperidone, dronabinol, fedotozine, fludorex, flumeridone, galdansetron, granisetron, itasetron, loxiglumide, lurosetron, meclizine, methallatal, metoclopramide, metopimazine, nabilone, naboctate, ondansetron, oxypendyl, palonsetron, pancopride, pipamazine, prochlorperazine, promethazine, scopolamine, sulpiride, thiethylperazine, thioproperazine, trimethobenzamide, tropisetron and zacoprid and their pharmaceutically acceptable salts or solvates. Particularly suitable anti-emetic and/or gastroprokinetic agents for use according to the invention include metoclopramide, cisapride, domperidone, and their

pharmaceutically acceptable salts or solvates. Metoclopramide is especially suitable. The anti-emetic and/or gastroprokinetic agents may be used alone or in combination with each other.

It will be appreciated by those skilled in the art that certain of the compounds described herein may exist in stereoisomeric forms (i.e. they may contain one or more asymmetric carbon atoms or may exhibit cis-trans isomerism). The individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention.

Analgesics that exist in enantiomeric forms include (S)-and (R)-naproxen ((S)- and (R)-2-(6-methoxy-2-naphthyl)propionic acid), (S)- and (R)-ibuprofen ((S)- and (R)-2-(4-(2-methylpropyl-phenyl)propionic acid), (S)- and (R)-flurbiprofen ((S)- and (R)- 2-(2-fluoro-biphenyl-4-yl-propionic acid), (S)- and (R)-ketoprofen ((S)- and (R)- 2-(3-benzylphenyl)propionic acid), (S)- and (R)-fenoprofen ((S)- and (R)- 2-(3-phenoxyphenyl)propionic acid), (S)- and (R)-tiaprofenic acid ((S)- and (R)-2-(5-benzyl-thien-2-yl)propionic acid), (S)- and (R)- sulindac ((S)- and (R)-(*Z*)-2-(5-fluor-2-methyl-1-(4-methylsulfinylbenzylidene)-inden-3-yl) acetic acid), (S)- and (R)-ketorolac ((S)- and (R)-5-benzoyl-2,3-dihydro-pyrrolizine-1-carboxylic acid), (S)- and (R)-azapropazone ((S)- and (R)-5-dimethylamino-9-methyl-2-propylpyrazolo-[1,2-a][1,2.4]benzotriazin-1,3(2H)-dione), and (S)- and (R)-etodolac ((S)- and (R)-1,8-diethyl-1,3,4,9-tetrahydropyrazolo[3,4-b]-indol-1-ylacetic acid).

Anti-emetic and/or gastroprokinetic agents that exist in enantiomeric forms include (S)- and (R)-alizapride ((S)- and (R)-6-methoxy-N-[[1-(2-propenyl)-2-pyrrolidinylmethyl-1H-benzotriazole-5-carboxamide), (S)- and (R)-azasetron ((S)- and (R)-6-chloro-3,4-dihydro-4-methyl-3-oxo-N-3-quinuclidinyl-2H-1,4-benzoxazine-8-carboxamide), (S)- and (R)-batanopride ((S)- and (R)-4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-[(1-methylacetonyl)oxy]benzamide), (S)- and (R)-benzquinamide ((S)- and (R)-2-(acetyloxy)-N,N-diethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2H-benzo[a]quinolizine-3-carboxamide, (S)- and (R)-

buclizine ((S)- and (R)-1-[(4-chlorophenyl)phenyl-methyl]-4-[[4-(1,1-dimethylethyl)phenyl]methyl]-piperazine, (S)- and (R)-cinitapride ((S)- and (R)-amino-N-[1-(3-cyclohexen-1-ylmethyl)-4-piperidyl]-2-ethoxy-5-nitrobenzamide), and (S)- and (R)-cisapride ((S)- and (R)-*cis*-4-amino-5-chloro-N-{1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidyl}-2-methoxybenzamide.

Compounds for use according to the invention may be administered simultaneously or sequentially and, when administration is sequential, the $5HT_1$ receptor agonist, analgesic and anti-emetic and/or gastroprokinetic agent may be administered in any order.

Compounds for use according to the invention may be administered as the raw material but the active ingredients are preferably provided in the form of pharmaceutical formulations.

The active ingredients may be used either as separate formulations or as a single combined formulation. When combined in the same formulation it will be appreciated that the active ingredients must be stable and compatible with each other and the other components of the formulation. Therefore, pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier comprise a further aspect of the invention. When formulated separately they may be provided in any convenient formulation, conveniently in such manner as are known for such compounds in the art.

When used according to the present invention, the $5HT_1$ receptor agonist is preferably other than zolmitriptan.

In a further embodiment of the invention, there is provided the use of a $5HT_1$ receptor agonist, or a pharmaceutically acceptable derivative thereof, as hereinbefore described, wherein the $5HT_1$ receptor agonist is sumatriptan. In a preferred embodiment, less than 100 mg of sumatriptan per unit dose is used.

In a particularly preferred embodiment, the analgesic is aspirin and the anti-emetic and/or gastroprokinetic agent is metoclopramide.

In a further aspect, the invention provides a method of treatment of a mammal, including a human, suffering from conditions associated with cephalic pain, comprising administering an effective amount of a pharmaceutical composition for oral administration comprising a $5HT_1$ receptor agonist, such as sumatriptan or naratriptan, or a pharmaceutically acceptable derivative thereof, with an analgesic, such as aspirin, naproxen, ibuprofen, paracetamol, or a pharmaceutically acceptable derivative thereof, and an anti-emetic and/or gastroprokinetic agent, such as metoclopramide, or a pharmaceutically acceptable derivative thereof. The analgesic is preferably aspirin.

In a further embodiment of the invention, there is provided a method of treatment, as hereinbefore described, wherein the $5HT_1$ receptor agonist is sumatriptan. In a preferred embodiment, less than 100 mg of sumatriptan per unit dose is used. In a particularly preferred embodiment, the analgesic is aspirin and the anti-emetic and/or gastroprokinetic agent is metoclopramide.

In a further embodiment of the invention, there is provided a method of treatment, as hereinbefore described, wherein the mammal is a human who has not responded to treatment using a $5HT_1$ receptor agonist alone.

In a further embodiment of the invention, there is provided a method of treatment, as hereinbefore described, wherein the mammal is a human who has not responded to treatment using an NSAID alone.

In a further aspect, the invention provides a pharmaceutical composition for oral administration for use in the treatment of conditions associated with cephalic pain, comprising a $5HT_1$ receptor agonist, such as sumatriptan or naratriptan, or a pharmaceutically acceptable derivative thereof, with an analgesic, such as aspirin, naproxen, ibuprofen, paracetamol, or a pharmaceutically acceptable

derivative thereof, and an anti-emetic and/or gastroprokinetic agent, such as metoclopramide, or a pharmaceutically acceptable derivative thereof. The analgesic is preferably aspirin.

In a further embodiment of the invention, there is provided a pharmaceutical composition, as hereinbefore described, wherein the $5HT_1$ receptor agonist is sumatriptan. In a preferred embodiment, less than 100 mg of sumatriptan per unit dose is used. In a particularly preferred embodiment, the analgesic is aspirin and the anti-emetic and/or gastroprokinetic agent is metoclopramide.

In a further aspect, the invention provides a pharmaceutical composition for oral administration for use in the treatment of conditions associated with cephalic pain comprising a $5HT_1$ receptor agonist, such as sumatriptan or naratriptan, or a pharmaceutically acceptable derivative thereof, with an analgesic, such as aspirin, naproxen, ibuprofen, paracetamol, or a pharmaceutically acceptable derivative thereof, and an anti-emetic and/or gastroprokinetic agent, such as metoclopramide, or a pharmaceutically acceptable derivative thereof, characterised in that the effective dose of $5HT_1$ receptor agonist is lower than when the $5HT_1$ receptor agonist is administered alone. The analgesic is preferably aspirin.

In a further embodiment of the invention, there is provided a pharmaceutical composition, as hereinbefore described, wherein the $5HT_1$ receptor agonist is sumatriptan. In a preferred embodiment, less than 100 mg of sumatriptan per unit dose is used. In a particularly preferred embodiment, the analgesic is aspirin and the anti-emetic and/or gastroprokinetic agent is metoclopramide.

In a further aspect, the invention provides a pharmaceutical composition for oral administration for use in the treatment of conditions associated with cephalic pain comprising a $5HT_1$ receptor agonist, such as sumatriptan or naratriptan, or a pharmaceutically acceptable derivative thereof, with an analgesic, such as aspirin, naproxen, ibuprofen, paracetamol, or a pharmaceutically acceptable

derivative thereof, and an anti-emetic and/or gastroprokinetic agent, such as metoclopramide, or a pharmaceutically acceptable derivative thereof, characterised in that the analgesic is used at a dose lower than that considered to produce an analgesic effect. The analgesic is preferably aspirin.

In a further embodiment of the invention, there is provided a pharmaceutical composition, as hereinbefore described, wherein the $5HT_1$ receptor agonist is sumatriptan. In a preferred embodiment, less than 100 mg of sumatriptan per unit dose is used. In a particularly preferred embodiment, the analgesic is aspirin and the anti-emetic and/or gastroprokinetic agent is metoclopramide.

In a further aspect, the invention provides a pharmaceutical composition for oral administration for use in the treatment of conditions associated with cephalic pain comprising a $5HT_1$ receptor agonist, such as sumatriptan or naratriptan, or a pharmaceutically acceptable derivative thereof, with an analgesic, such as aspirin, naproxen, ibuprofen, paracetamol, or a pharmaceutically acceptable derivative thereof, and an anti-emetic and/or gastroprokinetic agent, such as metoclopramide, or a pharmaceutically acceptable derivative thereof, characterised in that the effective dose of $5HT_1$ receptor agonist is lower than when the $5HT_1$ receptor agonist is administered alone and the analgesic is used at a dose lower than that considered to produce an analgesic effect. The analgesic is preferably aspirin.

In a further embodiment of the invention, there is provided a pharmaceutical composition, as hereinbefore described, wherein the $5HT_1$ receptor agonist is sumatriptan. In a preferred embodiment, less than 100 mg of sumatriptan per unit dose is used. In a particularly preferred embodiment, the analgesic is aspirin and the anti-emetic and/or gastroprokinetic agent is metoclopramide.

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms.

The $5HT_1$ receptor agonist, analgesic and anti-emetic and/or gastroprokinetic agent may be co-administered in the form of separate pharmaceutical compositions for simultaneous and/or sequential use. Preferably, the $5HT_1$ receptor agonist analgesic and anti-emetic and/or gastroprokinetic agent are administered as a single pharmaceutical composition for oral use comprising effective amounts of the active ingredients.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Thus, the ratio of $5HT_1$ receptor agonist to analgesic to anti-emetic and/or gastroprokinetic agent used in the uses, method or compositions according to the invention is in the range of 1 : 25 : 300 to 2 : 10000 : 5 to 400 : 10 : 1 (by weight), e.g. 1 : 20 : 12 to 10 : 2000 : 1 to 200 : 200 : 1, especially 5 : 9 : 1 or 10 : 9 : 1.

The amount of $5HT_1$ receptor agonist used according to the instant invention is preferably in the range of 0.2 to 200 mg per unit dose. For example, when sumatriptan is employed, the amount of sumatriptan in the composition is preferably in the range of 5 to 100 mg, more preferably 25 or 50 mg expressed as the weight of free base.

The amount of analgesic used according to the instant invention is preferably in the range of 5 to 1000 mg per unit dose. For example, when aspirin is employed, the amount of aspirin in the composition is preferably in the range of 100 to 1000 mg, more preferably 300 to 900 mg, such as 600 or 900 mg.

The amount of anti-emetic and/or gastroprokinetic agent used according to the instant invention is preferably in the range of 0.5 to 60 mg per unit dose. For example, when metoclopramide is employed, the amount of metoclopramide in the composition is preferably in the range of 1 to 60 mg, more preferably 2 to 20 mg, such as 5 or 10 mg.

The unit dose (for example contained in one tablet according to the invention) may be administered up to, for example, 6 times a day depending upon the unit dose used, the nature and severity of the conditions being treated, and the age and weight of the patient.

In the following examples, the $5HT_1$ receptor agonist may be replaced by any of the suitable $5HT_1$ receptor agonists described herein. Thus, for example, sumatriptan may be replaced by naratriptan, zolmitriptan, eletriptan, rizatriptan, frovatriptan, almotriptan, avitriptan, donitriptan, alniditan, ALX-0646, LY334370, U1092291, IS159 or PNY142633.

Additionally, the analgesic may be replaced by any of the suitable analgesics described herein. Thus, for example, aspirin may be replaced by naproxen, ibuprofen or paracetamol.

Additionally, the anti-emetic and/or gastroprokinetic agent may be replaced by any of the suitable anti-emetic and/or gastroprokinetic agents described herein. Thus, for example, metoclopramide may be replaced by cisapride or domperidone.

The $5HT_1$ receptor agonists, analgesic and anti-emetic and/or gastroprokinetic agents when used according to the instant invention may also be combined with other active agents.

The invention is further illustrated by the following non-limiting examples wherein the $5HT_1$ receptor agonist is sumatriptan, the analgesic is aspirin and the anti-emetic and/or gastroprokinetic agent is metoclopramide.

Example 1

20 patients suffering from acute migraine were treated with a combination of 100 mg sumatriptan, 900 mg aspirin and 10 mg metoclopramide. 65 % of patients were pain free within 2 hours of treatment.

Example 2

28 patients with a history of failed treatment with a $5HT_1$ receptor agonist alone and/or an NSAID alone and suffering from acute migraine were treated with a combination of 50 mg sumatriptan, 900 mg aspirin and 10 mg metoclopramide. 79 % of patients experienced headache relief within 2 hours of treatment.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any novel feature or combination of features described herein. This may take the form of product, composition, process or use claims and may include, by way of example and without limitation, one or more of the following claims:

Claims

1. The use of a $5HT_1$ receptor agonist, or a pharmaceutically acceptable derivative thereof, with an analgesic, or a pharmaceutically acceptable derivative thereof, and an anti-emetic and/or gastroprokinetic agent, or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for oral administration for use in the treatment of conditions associated with cephalic pain.

2. A method of treatment of a mammal, including a human, suffering from conditions associated with cephalic pain, comprising administering an effective amount of a pharmaceutical composition for oral administration comprising a $5HT_1$ receptor agonist, or a pharmaceutically acceptable derivative thereof, with an analgesic, or a pharmaceutically acceptable derivative thereof, and an anti-emetic and/or gastroprokinetic agent, or a pharmaceutically acceptable derivative thereof.

3. A pharmaceutical composition for oral administration for use in the treatment of conditions associated with cephalic pain, comprising a $5HT_1$ receptor agonist, or a pharmaceutically acceptable derivative thereof, with an analgesic, or a pharmaceutically acceptable derivative thereof, and an anti-emetic and/or gastroprokinetic agent, or a pharmaceutically acceptable derivative thereof.

4. A pharmaceutical composition for oral administration for use in the treatment of conditions associated with cephalic pain, comprising a $5HT_1$ receptor agonist, or a pharmaceutically acceptable derivative thereof, with an analgesic, or a pharmaceutically acceptable derivative thereof, and an anti-emetic and/or gastroprokinetic agent, or a pharmaceutically acceptable derivative thereof, characterised in that the effective dose of $5HT_1$ receptor agonist is lower than when the $5HT_1$ receptor agonist is administered alone.

5. A pharmaceutical composition for oral administration for use in the treatment of conditions associated with cephalic pain, comprising a $5HT_1$ receptor

agonist, or a pharmaceutically acceptable derivative thereof, with an analgesic, or a pharmaceutically acceptable derivative thereof, and an anti-emetic and/or gastroprokinetic agent, or a pharmaceutically acceptable derivative thereof, characterised in that the effective dose of analgesic is lower than when the analgesic is administered alone.

6. The use, method or pharmaceutical composition as claimed in any of Claims 1 to 5 wherein the condition associated with cephalic pain is migraine in a patient who has not responded to treatment using the $5HT_1$ receptor agonist alone.

7. The use, method or pharmaceutical composition as claimed in any of Claims 1 to 6 wherein the condition associated with cephalic pain is migraine in a patient who has not responded to treatment using the analgesic alone wherein the analgesic is an NSAID.

8. The use, method or pharmaceutical composition as claimed in any of Claims 1 to 7 wherein the $5HT_1$ receptor agonist is other than zolmitriptan.

9. The use, method or pharmaceutical composition as claimed in any of Claims 1 to 7 wherein the $5HT_1$ receptor agonist is sumatriptan or naratriptan, or a pharmaceutically acceptable derivative thereof.

10. The use, method or pharmaceutical composition as claimed in Claim 9 wherein the $5HT_1$ receptor agonist is sumatriptan, or a pharmaceutically acceptable derivative thereof.

11. The use, method or pharmaceutical composition as claimed in Claim 10 wherein less than 100 mg of sumatriptan per unit dose is used.

12. The use, method or pharmaceutical composition as claimed in any of Claims 1 to 7 wherein the analgesic is aspirin, naproxen, ibuprofen, or paracetamol, or a pharmaceutically acceptable derivative thereof.

13. The use, method or pharmaceutical composition as claimed in Claim 12 wherein the analgesic is aspirin or a pharmaceutically acceptable derivative thereof.

14. The use, method or pharmaceutical composition as claimed in Claim 12 wherein the analgesic is naproxen or a pharmaceutically acceptable derivative thereof.

15. The use, method or pharmaceutical composition as claimed in any of Claims 1 to 7 wherein the anti-emetic and/or gastroprokinetic agent is metoclopramide or a pharmaceutically acceptable derivative thereof.

16. The use, method or pharmaceutical composition as claimed in any of Claims 1 to 7 wherein the $5HT_1$ receptor agonist is sumatriptan or naratriptan, or a pharmaceutically acceptable derivative thereof, the analgesic is aspirin or a pharmaceutically acceptable derivative thereof, and the anti-emetic and/or gastroprokinetic agent is metoclopramide or a pharmaceutically acceptable derivative thereof.

17. The use, method or pharmaceutical composition as claimed in Claim 16 wherein the $5HT_1$ receptor agonist is sumatriptan, or a pharmaceutically acceptable derivative thereof, the analgesic is aspirin or a pharmaceutically acceptable derivative thereof, and the anti-emetic and/or gastroprokinetic agent is metoclopramide or a pharmaceutically acceptable derivative thereof.

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Published:
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: COMBINATIONS OF A 5HT1 RECEPTOR AGONIST WITH AN ANALGESIC, AND AN ANTI-EMETIC AND/OR A GASTROPROKINETIC AGENT

(57) Abstract: The present invention relates to the treatment of conditions associated with cephalic pain such as migraine, cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorders, headache associated with substances or their withdrawal, rebound headache and tension headache. In particular it relates to the use of a $5HT_1$ receptor agonist in combination with an analgesic and an anti-emetic and/or gastroprokinetic agent.

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/GB 02/00811

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61K31/60 A61P29/00 //(A61K31/60,31:445, 31:165),(A61K31/60,31:415,31:165)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 15275 A (ALGOS PHARMACEUTICAL) 16 April 1998 (1998-04-16) claims 1,2,7,13,22-24 page 15, line 8-23 examples 23,24	1-4,8-17
X	S.J.PEROUTKA: "Beyond monotherapy: rational polytherapy in migraine " HEADACHE, vol. 38, no. 1, 1998, pages 18-22, XP008012051 page 18, column 1 page 20	1-4, 6-10, 12-17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 January 2003	14/01/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Peeters, J

INTERNATIONAL SEARCH REPORT

national application No.
PCT/GB 02/00811

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: –
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 2,6-17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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Continuation of Box I.2

Present claims 1-8, relate to a product/compound/method defined by reference to a desirable characteristic or property, namely:
1) 5HT1 receptor agonist
2) Analgesic
3) Anti-emetic and/or gastroprokinetic agent

The claims cover all products/compounds/methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products/compounds/methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product/compound/method by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely claims 9-17 and for the compounds cited in the examples, with due regard to the general idea underlying the present application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

...ormation on patent family members

Inter ...onal Application No
PCT/GB 02/00811

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9815275 A	16-04-1998	US 5891885 A	06-04-1999
		AU 4806197 A	05-05-1998
		EP 0932416 A2	04-08-1999
		JP 2000508341 T	04-07-2000
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